Decision Summary

The Centers for Medicare and Medicaid Services (CMS) proposes that intracranial stenting with percutaneous transluminal angioplasty (PTA) is reasonable and necessary for the treatment of cerebral artery stenosis ≥ 50% in patients with intracranial atherosclerotic disease in the following circumstance:

> Intracranial stenting with PTA is reasonable and necessary when furnished in accordance with the Food and Drug Administration (FDA)-approved protocols governing Category B Investigational Device Exemption (IDE) clinical trials.

Except as set forth above, all other indications for PTA with or without stenting to treat obstructive lesions of the vertebral and cerebral arteries remain noncovered.

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Proposed Decision Memo

TO: Administrative File: CAG 00085R2
Intracranial Stenting

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SUBJECT: Proposed Decision Memorandum for Intracranial Stenting

DATE: August 9, 2006

I. Proposed Decision

The Centers for Medicare and Medicaid Services (CMS) proposes that intracranial stenting with percutaneous transluminal angioplasty (PTA) is reasonable and necessary for the treatment of cerebral artery stenosis $\geq$ 50% in patients with intracranial atherosclerotic disease in the following circumstance:

Intracranial stenting with PTA is reasonable and necessary when furnished in accordance with the Food and Drug Administration (FDA)-approved protocols governing Category B Investigational Device Exemption (IDE) clinical trials.

Except as set forth above, all other indications for PTA with or without stenting to treat obstructive lesions of the vertebral and cerebral arteries remain noncovered.

II. Background

Stenosis of the intracranial arteries accounts for about 8 to 10% of all ischemic strokes in the United States (Thijs et al., 2000). Of the 900,000 strokes or transient ischemic attacks (TIAs), about 70,000 to 90,000 are caused by intracranial arterial stenosis (Chimowitz et al., 2005). The major intracranial arteries include the anterior and middle cerebral arteries, the basilar artery and the intracranial segments of the vertebral artery. In previous instances (CAG#00085N), CMS has considered treatment of the internal carotid arteries grouped together with the intracranial arteries. In this analysis, CMS is evaluating stenting of the intracranial arteries separately since the treatment (angioplasty and stenting) of intracranial arterial stenosis is more technically difficult and has more inherent risks compared to carotid artery stenting

Medical therapy with antithrombotic agents such as aspirin and warfarin to reduce ischemic events has been the standard treatment for intracranial arterial stenosis. The recently completed Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial concluded that "aspirin should be used in preference to warfarin" (Chimowitz et al., 2005). The WASID trial was a well designed and conducted randomized trial and provided evidence of the outcomes of these patients on medical therapy. Even with aspirin therapy, the investigators reported a 15% probability of ischemic stroke, brain hemorrhage, or death from vascular causes other than stroke during 1 year of follow-up (Chimowitz et al., 2005). With the high risk of subsequent events, other approaches to patients with symptomatic intracranial arterial stenosis have been considered and studied. However, there have been no published trials on other medications or procedures compared to standard medical therapy.

In recent years, intracranial angioplasty with and without stent placement has been used in patients with significant intracranial arterial stenosis who either continue to have symptoms of a TIA or develop a stroke while on treatment with antithrombotic medications. A variety of stents have been placed in the intracranial arteries outside of their FDA-approved indication for use in other vessels of the body such as the coronary arteries. In 2005, the Boston Scientific Corporation received FDA approval of a Humanitarian Device Exemption (HDE[1]) application for the Wingspan Stent System with Gateway PTA Balloon Catheter (FDA- Boston Scientific Reconsideration Request Letter). The Wingspan Stent System is the first system specifically indicated for intracranial angioplasty and stenting.

On February 9, 2006, CMS accepted a formal request for a national coverage analysis for intracranial angioplasty and stenting with the Wingspan Stent System with Gateway PTA Balloon Catheter. Previously, CMS had issued national noncoverage determinations for "performance of PTA to treat obstructive lesions of the vertebral and cerebral arteries" because "the safety and efficacy of these procedures are not established" (Medicare NCD Manual Section 20.7). The request recommended the following language to replace the current noncoverage language:

Effective xxxxx, Medicare covers PTAand stenting of cerebral arteries when performed in vessels with greater than or equal to 50% stenosis for patients who are refractory to medical therapy, concurrent with use of a device approved for marketing by the FDA (subject to any requirements established by the applicable FDA approval or clearance process) for this specific indication.

III. History of Medicare Coverage

History of Medicare Coverage of Percutaneous Transluminal Angioplasty
Over the past six years, Medicare has expanded coverage for PTA, specifically of the carotid artery, but intracranial stenting has been nationally noncovered throughout this period. Medicare first covered PTA of the carotid artery concurrent with stent placement in accordance with the FDA approved protocols governing Category B IDE clinical trials and later in FDA required post approval studies (Medicare NCD Manual 20.7).

Current Medicare Coverage of Percutaneous Transluminal Angioplasty
Effective March 17, 2005, Medicare expanded coverage of PTA of the carotid artery when performed on patients who are at high risk for carotid endarterectomy (CEA) and also have symptomatic carotid artery stenosis $\geq$ 70% only when performed in a CMS approved facility for carotid artery stenting with FDA-approved carotid artery stenting systems and embolic protection devices.

PTA to treat obstructive lesions of the vertebral and cerebral arteries remained noncovered with the release of this NCD on March 17, 2005. Because of the existing noncoverage policy for PTA of the vertebral and cerebral arteries, the angioplasty would not be covered by Medicare for beneficiaries participating in FDA designated investigational device exemption (IDE) clinical trials.

Reconsideration
Boston Scientific Corporation requested that CMS reconsider the current coverage policy for intracranial stenting and angioplasty.

Benefit Category Determination
For an item or service to be covered by the Medicare program, it must meet one of the statutorily defined benefit categories outlined in the Social Security Act. Intracranial stenting and angioplasty may fall under the benefit category set forth in section §1861(b)(3) (inpatient hospital services), a part A benefit under §1812(a)(1) and §1861(s)(1) (physician services), a part B benefit. This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

IV. Timeline of Recent Activities

August 3, 2005	The FDA approves an HDE application for Boston Scientific Corporation's Wingspan Stent System with Gateway PTA Balloon Catheter.
February 9, 2006	CMS accepts Boston Scientific Corporation's formal NCD reconsideration request for coverage of intracranial stenting and angioplasty. The tracking sheet is posted and the initial 30-day comment period begins.
March 11, 2006	Initial 30-day public comment period closes. Comments are posted on website.

August 9, 2006	Proposed decision memorandum is posted and the 30-day public comment period begins.

V. FDA Status

On August 3, 2005, the Center for Devices and Radiological Health (CDRH) of the FDA completed its review and approved Boston Scientific Corporation's HDE application for the Wingspan Stent System with Gateway PTA Balloon Catheter. The CDRH stated that the "device is indicated for improving cerebral artery lumen diameter in patients with intracranial atherosclerotic disease, refractory to medical therapy, in intracranial vessels with greater than or equal to 50% stenosis that are accessible to the system" (FDA approval letter to Boston Scientific, 2005).

Since 1990, Congress has required the FDA to approve certain devices that are designed to treat or diagnose a disease or condition that affects fewer than 4,000 individuals in the United States. FDA categorizes these devices as Humanitarian Use Devices (HUD) and may provide a Humanitarian Device Exemption (HDE) that allows the device to be marketed for the limited condition. In order for the FDA to authorize the marketing of an HUD, the device manufacturer must submit an HDE application which has some similarity to a premarket approval (PMA) application, but need not present clinical data addressing the effectiveness of the device. Through the review of the application and information provided, the FDA must be able "to determine that the device does not pose an unreasonable or significant risk of illness or injury, and that the probable benefit to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment" (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfHDE/HDEInformation.cfm). In addition, the manufacturer must show that no comparable devices are available for treatment or diagnosis of the disease or condition, and there are no other means by which the device may be brought to market (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfHDE/HDEInformation.cfm). The device can have other indications and the affected population can be a small subset of a disease or condition. The HDE holder is required to ensure that an HUD approved device is only used in facilities having an Institutional Review Board (IRB) that continually reviews and approves the use of this device. In addition, the amount charged for the device cannot exceed the costs of the device's research, development, fabrication, and distribution. Finally, the FDA can require annual reports of the number of devices used to determine continued HUD status.

Through its review of Boston Scientific Corporation's HDE application and supporting materials, the "CDRH determined that, based on the data submitted in the HDE, the Wingspan Stent System with Gateway PTA Balloon Catheter will not expose patients to an unreasonable or significant risk of illness or injury, and the probable benefit to health from using the System for improving cerebral artery lumen diameter in patients with intracranial atherosclerotic disease, refractory to medical therapy, in intracranial vessels with $\geq$ 50% stenosis that are accessible to the system outweighs the risks of illness or injury" (FDA Summary of Safety and Probable Benefit, 2004).

The FDA's review concluded that the probable benefit of the System is an increase in diameter of atherosclerotic arteries, that all mechanical testing performed on the System met the acceptance criteria, and that the System was biocompatible. In addition, follow-up evaluation of animal testing showed no angiographic evidence of flow abnormalities or parent vessel stenosis. The CDRH also reviewed results from the Wingspan clinical study and concluded that "the type and frequency of observed adverse events including stroke are consistent with or lower than similar neurovascular procedures" (Summary of Safety and Probable Benefit). Thus, the CDRH concluded that the probable benefit outweighs the risk of injury or illness when the System is used according to the Instructions for Use.

CMS does not have a national policy that addresses coverage of HUDs. Currently, local contractors have discretion to provide coverage. However, an HUD is nationally noncovered if it falls under the purview of an NCD which nationally noncovers the device or service(s) for which the device may be used.

VI. General Methodological Principles

When making national coverage decisions, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that the agency utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in the Appendices. In general, features or clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, and the blinding of readers of the index test, and reference test results.

Public comments sometimes cite the published clinical evidence and give CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum.

VII. Evidence

A. Introduction

In this reconsideration, we considered studies and evidence that were published after the prior decision that addressed intracranial angioplasty and stenting in 2000. Health outcomes of interest include mortality, stroke, adverse events and restenosis (development of a new obstructive lesion in the treated segment). This National Coverage Analysis (NCA) focuses on the following question: "Is the evidence sufficient to conclude that balloon angioplasty and stenting using the Wingspan Stent System for intracranial artery stenosis $\geq$ 50%, refractory to medical therapy, will improve health outcomes for Medicare patients?"

B. Discussion of evidence reviewed

1. Literature Search

CMS searched PubMed (2000 to present) for publications of randomized clinical trials (RCTs), observational studies and reviews on intracranial angioplasty and stenting. General keywords included intracranial, angioplasty and stenting. Studies must have presented original data, examined primary health outcomes and been published in peer-reviewed English language journals. Abstracts were excluded.

2. External technology assessments and clinical reviews

Several review articles on intracranial angioplasty and stenting have been published. These articles were evaluated for additional evidence. If found then the original articles were included in our evidence and analysis sections.

3. Internal technology assessment

We retrieved 12 case series reports that met our search criteria. We also reviewed the FDA Summary of Safety and Probable Benefit for the Wingspan system. We did not find any clinical trial (randomized or nonrandomized) that compared angioplasty and stenting to medical therapy. Since no comparative trial was identified, we expanded our search to include medical therapies to provide a basis for the natural history of symptomatic intracranial arterial stenosis. One trial was found and reviewed.

A. Medical Therapy

Chimowitz MI, Lynn MJ, Howlett-Smith H, et al. Comparison of warafin and aspirin for symptomatic intracranial arterial stenosis. N Engl J Med 2005;352:1305-1316.

Chimowitz and colleagues reported the results of a randomized double blind, multicenter trial, known as WASID, to compare aspirin with warfarin in patients with symptomatic intracranial arterial stenosis. Inclusion criteria included patients with TIAs or nondisabling stroke, angiographically verified stenosis of 50% to 99% of a major intracranial artery (carotid, middle cerebral, vertebral, or basilar), a modified Rankin score of 3 or less, and age $\geq$ 40 years. The primary end point was a composite of ischemic stroke, brain hemorrhage, or death from vascular causes other than stroke. After 569 patients were randomly assigned to aspirin (n=280) or warfarin (n=289), enrollment was stopped due to safety concerns of patients who received warfarin. There were 350 men and 219 women. Mean age was about 63 years. Mean follow-up time was 1.8 years. Although the primary end point at the stopping time did not differ significantly, patients who received warfarin had significantly higher rates of death (9.7% vs. 4.3%), major hemorrhage (8.3% vs. 3.2%), and myocardial infarction or sudden death (7.3% vs. 2.9%) compared to aspirin, respectively. The investigators noted: "Warfarin was associated with significantly higher rates of adverse events and provided no benefit over aspirin in this trial."

The WASID trial was a well designed, well conducted, randomized comparison trial that provided evidence on the outcomes of patients with symptomatic intracranial arterial stenosis who were treated with aspirin or warfarin. As noted by the WASID investigators, the 1 year probability of the primary end point was 0.15 for patients who received aspirin and 0.17 for patients who received warfarin. This analysis provides information on the natural history of this disease for patients on these medications and a baseline of comparison for other more invasive treatments and interventions.

B. Intracranial angioplasty and stenting

Levy EI, Ecker RD, Horowitz MB, et al. Stent-assisted intracranial recanalization for acute stroke: early results. Neurosurgery 2006;58(3):458-463.

Levy and colleagues reported the results of a case series of 19 patients who underwent intracranial stenting after failed pharmacologic and/or mechanical thrombolysis in the setting of an acute ischemic stroke. The patients were treated from 07/2001 to 03/2005 at the University of Buffalo and the University of Pittsburgh. Inclusion criteria were not further specified. Data were abstracted retrospectively from facility inpatient records. There were 13 men (68%) and 6 women with a mean age of 60 years. Overall recanalization rate was 79%. There were 6 deaths (31.5%) and 1 intracranial hemorrhage during the hospitalization. Long term follow-up was not reported. Three different balloon expandable stents (Vision, BiodivYsio, Driver) were used. Patients received clopidogrel (1 month) and aspirin (indefinite period) after the procedure. The authors noted: "Stent-assisted recanalization for acute stroke resulting from intracranial thrombotic occlusion is associated with a high recanalization rate and low intracranial hemorrhage rate."

Kessler IM, Mounayer C, Piotin M, et al. The use of balloon-expandable stents in the management of intracranial arterial diseases: a 5-year single-center experience. AJNR Am J Neuroradiol 2005;26(9):2342-2348.

Kessler and colleagues reported the results of a case series of 75 patients who underwent intracranial stenting for intracranial aneurysms and atherosclerotic stenosis. The patients were treated from 1998 to 2003 at 1 facility in France. Data were abstracted retrospectively from facility inpatient records. Of the 75 patients, 16 were treated for stenosis with 4 receiving angioplasty prior to stent placement. Inclusion criteria included stenosis of 60% or more by angiogram, associated with recurrent symptoms despite antiplatelet treatment. There were 14 men (88%) and 2 women with a mean age of 62 years. Procedural success rate was 81.2%. Median stenosis was reduced from 84% to 12%. Balloon expandable stents were used (Cerebrence, AVE, S670, CrossFlex, Express). Median follow-up period was 6 months. There was 1 death, 3 subarachnoid hemorrhages, and 1 stroke out of the 16 patients (25%) that received stenting. Patients received clopidogrel and aspirin for at least 1 month. The authors noted: "The use of BES is associated with a high rate of hemorrhagic and ischemic complications, more specifically when used in the anterior circulation."

Abou-Chebl A, Bashir Q, Yadav JS. Drug-eluting stents for the treatment of intracranial atherosclerosis: initial experience and midterm angiographic follow-up. Stroke 2005;36(12):e165-8. Epub 2005 Nov 10.

Abou-Chebl and colleagues reported the results of a case series of 8 patients who underwent intracranial angioplasty and stenting with drug-eluting stents (Cypher, Taxus) at the Cleveland Clinic Foundation. Inclusion criteria included intracranial stenosis > 70% and failed medical therapy (antithrombotic agents). There were 6 men (75%) and 2 women with a mean age of 66 years. Procedural success rate was 100%. Mean stenosis was reduced from 84% to 2.5%. Mean follow-up period was 11 months. There were no deaths, 1 retinal embolism and 1 basilar artery dissection. Patients received clopidogrel and aspirin for 1 year. The authors noted: "Elective intracranial stenting with DES appears to be feasible and safe, but additional clinical experience is required to assess its efficacy."

Henkes H, Miloslavski E, Lowens S, et al. Treatment of intracranial atherosclerotic stenoses with balloon dilatation and self-expanding stent deployment (WingSpan). Neuroradiology 2005;47(3):222-8. Epub 2005 Mar 15.

Henkes and colleagues reported the results of a case series of 15 patients who underwent intracranial angioplasty and stenting with a self-expanding stent (Wingspan) at the University Duisburg-Essen in Germany. Inclusion criteria included intracranial arterial stenosis > 50%, symptoms under medical therapy and brain ischemia attributable to the stenosis. There were 10 men (67%) and 5 women with a mean age of 64 years. Procedural success rate was 100%. Mean stenosis was reduced from 72% to 38% after stent deployment. There were no deaths and 1 post procedural stroke (6.7% procedural death and stroke rate). There were no other deaths and strokes at the 4 week follow-up. Patients received clopidogrel and aspirin for 2 months. At 6 months, 12 of the 37 (32%) patients had developed restenosis $\geq$ 50%. The authors noted: "The high success and low complication rate in this series are partly due to the desirable physical properties of the device under investigation. Safety and efficacy may, however, vary significantly with both experience and skills of the operator and familiarity of the operator with the device."

Kim DJ, Lee BH, Kim DI, et al. Stent-assisted angioplasty of symptomatic intracranial vertebrobasilar artery stenosis: feasibility and follow-up results. AJNR Am J Neuroradiol 2005;26:1381-1388.

Kim and colleagues reported the results of a case series of 17 patients who underwent intracranial angioplasty and stenting using coronary stents. Patients were treated from 2000 to 2004 at 4 facilities in Korea. Inclusion criteria included recurrent symptoms due to vertebrobasilar artery stenosis while on antiplatelet and anticoagulation medications, and atherosclerotic stenoses > 50% by angiogram that were responsible for the symptoms. There were 10 men (59%) and 7 women. Mean age was 64 years. Procedural success was 100%. Various balloon expandable stents were used (S660, S670, JoFlex, AVE, Cypher). Mean stenosis was reduced from 76% to 1.3%. Mean follow-up period was 17 months. There were no deaths or inhospital strokes reported. Patients received clopidogrel and aspirin indefinitely. The author noted: "Stent-assisted angioplasty is a feasible treatment method for vertebrobasilar artery stenosis. The patency of the stent-assisted angioplasty seems to be preserved in the long-term, with good clinical outcome."

Straube T, Stingele R, Jansen O. Primary stenting of intracranial atherosclerotic stenoses. Cardiovasc Intervent Radiol 2005;28:289-295.

Straube and colleagues reported the results of a case series of 12 patients who underwent intracranial angioplasty and stenting using coronary stents. Patients were treated from 2001 to 2002 at the University of Kiel in Germany. Inclusion criteria included patients with symptomatic intracranial stenosis of 50%-99% for treatment of acute thrombosis or to decrease risk after failed antithrombotic therapy. There were 6 men and 6 women enrolled. Mean age was 64 years. Stenting was successful in 11 of 12 patients. Balloon expandable stents (S660, S7) or a carotid stent (Wallstent) were used. All patient received aspirin and clopidogrel (at least 4 weeks). Mean follow-up period was 4 months. There were 3 deaths (25% - all of the patients with acute thrombosis). The authors noted: "Prophylactic primary stenting of intracranial stenoses of the anterior or posterior cerebral circulation can be performed with a low complication rate; technical problems such as stent flexibility must still be solved."

Lylyk P, Vila JF, Miranda C, et al. Endovascular reconstruction by means of stent placement in symptomatic intracranial atherosclerotic stenosis. Neurol Res 2005;27 Suppl 1:S84-8 (includes patients reported in Lylyk et al. Angioplasty and stent placement in intracranial atherosclerotic stenosis and dissections. AJNR Am J Neuroradiol 2002;23:430-436).

Lylyk and colleagues reported the results of a case series of 104 patients who underwent stent-assisted angioplasty for symptomatic intracranial atherosclerotic stenosis despite medical therapy. The patients were treated from 1996 to 2004 at the Clinica Medica Belgrano in Argentina. Inclusion criteria included symptomatic stenosis 50-99% on angiogram and ischemic events on antithrombotic therapy. The numbers of men and women were not reported. Mean age was 67 years. Procedural success was 98%. Various balloon expandable stents were used (AVE, Velocity, Penta, others). Mean stenosis was reduced from 75.4% to 18%. Follow period ranged from 3 to 6 months. The overall mortality rate was 14.4% and neurological procedure-related mortality rate was 3.8%. Restenosis rate was 12.5% (unspecified time frame). Patients received clopidogrel and aspirin for at least 3 months. The authors noted: "In selected patients, endovascular revascularization of intracranial arteries by means of stent-assisted angioplasty is technically feasible, effective, and safe."

Hatano T, Tsukahara E, Ogino E, et al. Stenting for vertebrobasilar artery stenosis. Acta Neurochir 2005;94:137-141.

Hatano and colleagues reported the results of a case series of 101 patients who underwent intracranial angioplasty and stenting for symptomatic vertebral artery ostial stenosis and 15 patients for vertebrobasilar artery stenosis. The patients were treated from 1997 to 2004 at the Kyoto Medical Center in Japan. Inclusion criteria included symptomatic stenosis > 60% by angiogram. There were 97 men (84%) and 19 women with a mean age of about 70 years. Dilatation was successful in 115 patients (99%). Various balloon expandable stents were used (Palmaz, S670, S660). The stenosis rate was reduced from 81% to 2% in patients with ostial stenosis and from 84% to 16% in patients with vertebrobasilar stenosis. Patients received aspirin and ticlopidine for at least one week before and 4 weeks after the procedures. There were no deaths and 1 major stroke. Restenosis was 12% (4.5% after 2001) and 27%, respectively. Follow up period was at least 6 months. The authors noted: "Stenting for vertebrobasilar artery stenosis is feasible and safe. Prevention of restenosis, especially in intracranial arteries, is the next problem to be solved."

FDA. Wingspan Summary of Safety and Probable Benefit. 2004

As part of the documentation for the Wingspan system (Humanitarian Device Exemption H050001), a case series of 45 patients who underwent angioplasty and stenting was reported in the FDA Summary of Safety and Probable Benefit (http://www.fda.gov/cdrh/mda/docs/h050001.html). Inclusion criteria included recurrent stroke, refractory to medical therapy, and symptomatic intracranial stenosis $\geq$ 50%. There were 33 men and 12 women. Mean age was 66 years. Average stenosis was not reported. Angioplasty and stenting were successful in 44 patients performed at 12 facilities. At 30 days, there were 1 death and 2 strokes (6.7% death and stroke). At 6 months, there were 1 death and 4 strokes (11%).

Jiang WJ, Wang YJ, Bin D, et al., Stenting of symptomatic MI stenosis of middle cerebral artery. Stroke 2004;35:1375-1380.

Jiang and colleagues reported the results of a case series of 40 patients who underwent intracranial angioplasty and stenting for symptomatic stenosis of the middle cerebral artery. The patients were treated from 2002 to 2003 at the Beijing Tiantan Hospital in China. Inclusion criteria included symptomatic stenosis ≥ 50% refractory to medical therapy. There were 31 men (78%) and 9 women with a mean age of about 42 years. The success rate was 98%. BiodivYsio and S660 stents were used. Mean stenosis was reduced from 80% to 5%. Median follow-up period was 10 months. There was 1 death (2.5%). The complication rate was 10%. The authors noted: "Stenting appears to be an effective and feasible therapy for symptomatic MI stenoses, but also appears to have the higher periprocedural complications, which need strict procedural and periprocedural management to reduce the mortality and morbidity."

SSLYVIA Investigators. Stenting of symptomatic atherosclerotic lesions in the vertebral or intracranial arteries (SSYLVIA) study results. Stroke 2004;35:1388-1392.

The SSLYVIA investigators reported the results of a case series of 61 patients who underwent angioplasty and stenting for symptomatic atherosclerotic disease of the extracranial vertebral and intracranial arteries. Patients were treated from 2000 to 2001 at several facilities in Europe and the U.S. Inclusion criteria included TIA or stroke due to a single atherosclerotic stenosis ≥ 50% of an extracranial vertebral or intracranial artery by angiography. There were 50 men (82%) and 11 women. Mean age was 64 years. There were 43 intracranial arteries (15 internal carotid, 5 middle cerebral, 1 posterior cerebral, 17 basilar, 5 vertebral) and 18 extracranial vertebral arteries (6 ostia, 12 proximal to the posterior inferior cerebellar artery) treated using the NEUROLINK System (Guidant). The stent was successfully placed in 58 of the 61 patients (95%). Aspirin and clopidogrel were given before the procedures and continued for at least 1 year and 4 weeks, respectively. At 30 days, there were no deaths and 4 strokes. At 1 year, there were 8 strokes. Restenosis occurred in 35% of patients. The investigators reported that "strokes occurred in 6.6% of patients within 30 days and in 7.3% between 30 days and 1 year."

Gomez CR, Misra VK, Liu MW, et al. Elective stenting of symptomatic basilar artery stenosis. Stroke 2000;31:95-99.

Gomez and colleagues reported the results of a case series of 12 patients who underwent stenting of the basilar artery for vertebrobasilar ischemia after failed medical therapy. Patients were treated from 1998 to 1999 at the University of Alabama at Birmingham. Inclusion criteria included basilar artery stenosis > 50% by angiogram, and recurrent symptoms on heparin or warfarin. There were 10 men and 2 women. Mean age was 63 years. Angioplasty and stent placement (coronary stents – Microstent, GFX, Multilink Duet) was successful in all patients. Mean stenosis decreased from 71.4% to 10.3%. Mean follow-up was 5.9 months. There were no deaths or strokes. One patient had a transient ischemic attack and 1 had dizziness. The authors reported: "Elective stenting of the basilar artery is feasible, with minimal risk to the patient. Its impact on long-term stroke prevention and its durability are unknown and will require further study."

Mori T, Kazita K, Chokyu K, et al. Short-term arteriographic and clinical outcome after cerebral angioplasty and stenting for intracranial vertebrobasilar and carotid atherosclerotic occlusive disease. AJNR Am J Neuroradiol 2000;21:249-254.

Samuels and colleagues reported the results of a case series of 10 patients who underwent stenting for intracranial and carotid artery stenosis. Patients were treated in 1998 at the Kochi Medical School Hospital in Japan. Inclusion criteria included stenosis $\geq$ 60% and symptoms unresponsive to medical therapy. There were 9 men and 1 woman. Mean age was 68 years. Stents were placed successfully in 8 of the 10 patients. Mean stenosis was reduced from about 80% to 7% using coronary stents (GFX, Multilink). Average follow-up period was 11 months. There were no deaths or strokes. The authors noted: "CAS (cerebral angioplasty and stenting) appears to be a safe and effective means for treating intracranial atherosclerotic occlusive disease, yielding a favorable arteriographic and clinical outcome."

4. MCAC

Not applicable.

5. Guidelines

Not applicable.

6. Professional Society Position Statements

The American Society of Interventional and Therapeutic Neuroradiology (ASITN), Society of Interventional Radiology (SIR), and American Society of Neuroradiology (ASNR) issued the following joint position statement supporting the use of and insurance coverage for intracranial stenting and angioplasty for intracranial atherosclerosis.

(1) For symptomatic patients with a > 50% intracranial stenosis who have failed medical therapy, balloon angioplasty with or without stenting should be considered.

(2) Patients who have an asymptomatic intracranial arterial stenosis should first be counseled regarding optimizing medical therapy. There is insufficient evidence to make definitive recommendations regarding endovascular therapy in asymptomatic patients with severe intracranial atherosclerosis. They should be counseled regarding the nature and extent of their disease, monitored for new neurological symptoms, and have periodic non-invasive imaging at regular intervals of 6 to 12 months (magnetic resonance angiography or computed tomographic angiography) initially, and then by cerebral angiography if warranted. At a minimum, optimal prophylactic medical therapy should be instituted, which might include antiplatelet and/or statin therapy.

(3) Continued evaluation and improvements in both pharmacological and catheter-based therapies are needed to reduce the strokeburden from intracranial atherosclerosis (Higashida et al, 2005).

The societies conclude by recommending "reimbursement by third party insurers so that those patients may have access to such interventions" (Higashida et al., 2005).

7. Expert Opinion

Not applicable.

8. Public Comments

The Centers for Medicare and Medicaid Services received 140 comments during the initial 30-day comment period. The majority of these comments were generated from a public comment template made available to interested parties by the requestor; therefore, much of the evidence discussed and statements of support were identical. When reviewing public comments, CMS focuses on the quality of data and evidence references rather than the quantity of comments submitted. If published studies were provided that had not been previously identified, the additional data were incorporated in this evidence section.

Comments with Evidence

American Heart Association Heart and Disease Stroke Statistics: 2005 Update. Dallas TX: American Heart Association. 2005; page 2.
Twenty nine (29) commenters cite the 2005 update of heart and stroke statistics to describe the role of intracranial atherosclerotic disease in the occurrence of stroke and subsequent death and disability as well as the negative economic impact the disease has in the United States.

Kasner et al. Predictors of Ischemic Stroke in the Territory of a Symptomatic Intracranial Arterial Stenosis. Circulation. 2006;113:555-563.
Thirty one (31) commenters cite this study to support their assertion that medical management of intracranial atherosclerotic disease is not an effective treatment for many patients.

Chimowitz et al. The Warfarin-Aspirin Symptomatic Intracranial Disease Study. Neurology. 1995; 45:1488-1493.
The EC/IC Bypass Study Group. Failure of Extracranial-Intracranial Arterial Bypass to Reduce the Risk of Ischemic Stroke. Results of an interventional randomized trial. NEJM. 1985;313: 1191-1200.
Twenty eight (28) commenters cite these studies to further support their assertion that medical management of ICAD patients is not an effective treatment option. They also cite these studies to support their affirmation that ICAD patients do not have access to effective treatment options due to the national noncoverage policy for intracranial stenting which prohibits Medicare coverage of intracranial stenting and angioplasty. Since intracranial stenting and angioplasty is not covered by Medicare, patients are limited to covered treatments like medical management, which these commenters conclude to be ineffective.

Chimowitz MI et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. NEJM. 2005;352:1350-16.
Three commenters cite this article to support the need for more effective treatment options since medical management of ICAD patients is shown to be unsatisfactory.

Thijs VN, Albers GW. Symptomatic intracranial atherosclerosis outcome of patients who fail antithrombotic therapy. Neurology. 2000;55:490-7.
Four commenters cite this article to demonstrate the need for expedited coverage of intracranial stenting due to ineffectiveness of medical therapy.

Albers et al., Stanford.
One commenter cites this article to demonstrate the need for coverage of intracranial stenting due to high stroke rates in posterior circulation in symptomatic and asymptomatic patients.

Schumacher HC et al. Intracranial Angioplasty and Stent Placement for Cerebral Atherosclerosis. Journal of Vascular and Interventional Radiology. 2004;15:S123-S132.
Twenty Eight (28) commenters cite this study to establish the significant advances in intracranial stenting and angioplasty over the past decade. They assert that intracranial stenting and angioplasty has become a promising therapy in symptomatic patients with high grade stenosis who do not respond to medical therapy.

Hartman M et al. One Year Stroke Risks in High Grade, Symptomatic, Medically Refractory Intracranial Atherosclerosis after Angioplasty and Stenting: The Wingspan Trial. Poster Presentation. International Stroke Conference 2006. American Stroke Association. February 2006.
Thirty three (33) commenters cite the Wingspan study to demonstrate the safety and effectiveness of the Wingspan Stent System with Gateway PTA Balloon Catheter in treating medically refractory patients with intracranial atherosclerotic lesions $\geq$50% stenosis.

Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVIA): study results. Stroke. 2004;35:1388-92.
Jiang, WJ, Wang YI, et al. Stenting of symptomatic MI stenosis of middle cerebral artery: an initial experience of 40 patients. Stroke. 2004;35:1375-80.
Two commenters cite these studies to support their assertion that intracranial stenting is safe and effective.

Rasmussen P. Evidence-based Management of Cerebrovascular Disease. Case discussion on early U.S. experience at three institutions: Cleveland Clinic, Barrow Neurological Institute, and SUNY Buffalo. International Stroke Conference 2006. American Stroke Association. February 17, 2006.
Twenty nine (29) commenters cite this discussion to identify the similar success rate of the Wingspan HDE trial to early U.S. experience with intracranial stenting.

Higashida et al. Intracranial Angioplasty and Stenting for Cerebral Atherosclerosis: Current Position Statement of the American Society of Interventional and Therapeutic Neuroradiology (ASITN), the Society of Interventional Radiology (SIR), and the American Society of Neuroradiology (ASNR). Journal of Vascular and Interventional Radiology. October 2005;16(10):1281-85. and *American Journal of Neuroradiology. 2005;26:2323-2327.*
Twenty six (26) commenters cite this joint position statement supporting health insurance coverage for symptomatic medically refractory ICAD patients.

42 U.S.C. § 1395y(a)(1)(A); 68 FR 55634, September 26, 2003.
The reconsideration requestor, Boston Scientific Corporation, cites these publications as statutes under which coverage of intracranial stenting and angioplasty should be extended. Specifically, they refer to 68 FR 55634, September 26, 2003 in which the determination of whether an item is reasonable and necessary (42 U.S.C. § 1395y(a)(1)(A)) may be based on variable evidence depending on the condition in question.

Comments without Evidence
Thirty five (35) commenters cite heart and stroke statistics to describe the danger of intracranial atherosclerotic disease and the role ICAD plays in the occurrence of stroke and subsequent death and disability. In addition, the statistics describe the negative economic impact ICAD has in the United States.

Forty nine (49) commenters discuss the ineffectiveness of currently utilized and covered treatment options for ICAD patients. They assert that medical therapy and other treatments have been shown to be ineffective in some patients leaving them with no options due the CMS' noncoverage policy.

Thirty three (33) commenters assert that during the past decade intracranial stenting and angioplasty has become a promising therapy for symptomatic ICAD patients with high grade stenosis who fail medical therapy.

Forty (40) commenters stress that the positive Wingspan study results support coverage for intracranial stenting and angioplasty. In addition, 30 commenters describe U.S. experience with Wingspan as very similar to that found in the Wingspan study.

Thirty two (32) commenters state that intracranial stenting and angioplasty should be covered by Medicare and support this with a joint position statement supporting insurance coverage issued by ASITN, SIR, and ASNR. However, one commenter states that these supportive positions are premature and potentially self-serving in nature.

Of the comments received, 44 support coverage of intracranial stenting and angioplasty. Seventy five (75) commenters request coverage of intracranial stenting and PTA with the Wingspan Stent System with Gateway PTA Balloon Catheter specifically. Seventy six (76) commenters request that Medicare cover PTA and stenting in intracranial vessels with $\geq$50% stenosis in patients refractory to medical therapy, concurrent with the FDA indications for use. Six commenters specifically call for coverage of symptomatic ICAD patients with > 50% stenosis who do not respond to medical therapy. One commenter states that symptomatic patients with > 50% stenosis and asymptomatic patients with > 80% stenosis should be covered by Medicare. One commenter contends that coverage should be available for 1) symptomatic intracranial stenosis; 2) bailout for intracranial angioplasty with acute or subacute thrombosis; 3) acute stroke in cases where approved therapies failed; and 4) high grade symptomatic stenosis $\geq$75% where perfusion imaging has shown a significant perfusion deficit in that vessel territory.

Coverage of intracranial PTA and stenting in Category B IDE trials is requested by 75 commenters. Currently, the PTA and stent are not covered in Category B IDE trials. Three commenters support coverage of intracranial stenting and angioplasty when patients are part of a study or registry. One commenter asserts that careful regulations must accompany coverage of intracranial stenting and angioplasty.

Of the comments received, 70 state that the national noncoverage policy for intracranial stenting and angioplasty places a financial burden on hospitals which prevents them from providing this treatment. Five commenters note that the noncoverage policy prevents physicians from providing appropriate and beneficial therapy while 24 commenters state that the policy limits patients' treatment options and access. Sixty (60) commenters attest that there is currently enough evidence to warrant Medicare coverage for this procedure. Seven commenters state that studies support Medicare coverage, while two commenters assert that studies to date have been inadequate or resulted in unfavorable outcomes.

Finally, three commenters request that Medicare cover balloon dilation for vasospasm because they believe it is inappropriately noncovered under this noncoverage policy.

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member" (§ 1862(a)(1)(A)).

In analyzing the evidence, CMS asked: "Is the evidence sufficient to conclude that balloon angioplasty and stenting using the Wingspan system for intracranial artery stenosis $\geq$ 50%, refractory to medical therapy, will improve health outcomes for Medicare patients?" In our review, we evaluated 12 case series studies on intracranial angioplasty and stenting. As noted in the Appendices, case series type studies provide weak evidence, in general, due to inherent methodological shortcomings. We did not find any randomized trials (published or presented) on intracranial angioplasty and stenting. We also did not find any study that compared intracranial angioplasty and stenting to other treatments or optimal medical therapy.
Of the 12 case series, only 1 (Henkes) studied the Wingspan Stent system. This study had a small sample size of 15 patients and only a 4 week follow-up period. By itself, the study by Henkes provides insufficient evidence.

In the FDA Summary of Safety and Probable Benefit, data from a case series of 45 patients were presented. This comprises the total available data on intracranial angioplasty and stenting using the Wingspan system. The evidence on the Wingspan system is very limited (45 to 60 patients - it is unclear if there is overlap of the patients in Henkes study and the data presented to the FDA). In addition to the small sample sizes, short term follow-up and weak study design, the death and stroke rate for patients who underwent intracranial angioplasty and stenting using the Wingspan system was high (6.7% at 30 days in Henkes study and 11.9% at 6 months in the FDA submission). The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial showed a comparable 1 year probability of 15% for ischemic stroke, hemorrhage or death for patients with symptomatic intracranial artery stenosis that were treated with aspirin (Chimowitz et al., 2006) without the acute risks seen for angioplasty with stenting. The similarity of results was noted by both the WASID and Wingspan investigators. The WASID investigators reported: "Notably, the point estimates of the 1 year rates of stroke in WASID and SSYLVIA were virtually identical" (Kasner et al., 2006). The Wingspan investigators reported: "From the small number of patients studied, it appears that the Wingspan study results are similar to those reported for the SSLYVIA study" (FDA SSE, 2005).

The 11 remaining case series studied intracranial angioplasty and stenting using stents that were originally FDA approved for use in the coronary arteries. Since these stents are considerably different than the Wingspan self expanding stent, these studies do not provide supporting evidence for the Wingspan system. While several of the case series studies demonstrated improvements in lumen diameter after angioplasty and stenting, these findings alone are insufficient to support coverage without limitations. As the FDA noted, increases in diameter of atherosclerotic arteries may indicate probable benefit.

Based on the available data, CMS has determined that there is insufficient evidence to conclude that angioplasty and stenting using the Wingspan Stent system for intracranial artery stenosis $\geq$ 50%, refractory to medical therapy, will improve health outcomes for Medicare patients in general without limitations. However, since the FDA has approved an HDE application for PTA and stenting using the Wingspan system, CMS has determined that it is reasonable and necessary for the treatment of cerebral artery stenosis $\geq$ 50% in patients with intracranial atherosclerotic disease in the following circumstance:

Intracranial stenting with PTA is reasonable and necessary when furnished in accordance with the Food and Drug Administration (FDA)-approved protocols governing Category B Investigational Device Exemption (IDE) clinical trials.

After a complete review of the scientific and clinical evidence regarding intracranial artery angioplasty-stenting, it is clear that PTA concurrent with stent placement is a different procedure than stand-alone PTA of the intracranial artery, the procedure that was the basis for the previous national noncoverage policy. We have determined that although a body of evidence (primarily case series and single-center experiences) has been published and suggests a potential benefit to some patients, there is not sufficient information to: (1) predict the effect of generalized use of intracranial artery stenting; (2) to evaluate the long-term outcomes of this therapy; and, (3) to determine the appropriate patient groups that may benefit. We do not believe a national coverage policy without restrictions is appropriate at this time for this procedure. However, we do believe that the available evidence regarding intracranial artery stenting concurrent with angioplasty, and the FDA's willingness to approve the HDE status of the Wingspan intracranial artery stent, are sufficient to indicate that intracranial artery angioplasty, when performed concurrent with stenting, is a reasonable and necessary service if provided in a Category B IDE trial

There are a number of questions that remain to be answered. The safety and effectiveness of intracranial angioplasty and stenting have yet to be fully determined. The type of patient that should undergo intracranial angioplasty and stenting has not been appropriately identified. The various case series studies had different inclusion criteria and requirements of degree of stenosis and location. The type of stent that is best suited for the intracranial arteries has not been clearly defined. Various coronary balloon expandable stents, drug eluting coronary stents and the Wingspan self expanding stent were used in the case series reports with inconsistent and inconclusive results. The role of optimal medical therapy using anticoagulants and newer antiplatelet agents such as ticlopidine and clopidogrel has not been fully studied. Ultimately a well designed, well conducted, randomized controlled trial of intracranial angioplasty and stenting compared to optimal medical therapy is needed. This is consistent with current expert opinions of the WASID investigators who further noted: "Given the inherent risks of intracranial stenting, it is likely that the role, if any, for stenting will emerge from randomized controlled trials of patients at particularly high risk of stroke in the territory despite medical treatment" (Kasner et al., 2006).

CMS is also considering expansion of coverage for humanitarian use devices such as the Wingspan stent system in the separate reconsideration of the Clinical Trial Policy (CAG-00071R) under section 1862(a)(1)(E) of the Social Security Act. The tracking sheet announcing the reconsideration of the Clinical Trial Policy can be found at http://www.cms.hhs.gov/mcd/viewnca.asp?where=index&nca_id=186&basket=nca:00071R:186:Clinical+Trial+Policy:Open:1st+Recon:1.

IX. Proposed Decision

The Centers for Medicare and Medicaid Services (CMS) proposes that intracranial stenting with percutaneous transluminal angioplasty (PTA) is reasonable and necessary for the treatment of cerebral artery stenosis $\geq$ 50% in patients with intracranial atherosclerotic disease in the following circumstance:

Intracranial stenting with PTA is reasonable and necessary when furnished in accordance with the Food and Drug Administration (FDA)-approved protocols governing Category B Investigational Device Exemption (IDE) clinical trials.

Except as set forth above, all other indications for PTA with or without stenting to treat obstructive lesions of the vertebral and cerebral arteries remain noncovered.

Appendix A: General Methodological Principles of Study Design

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine whether: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

CMS normally divides the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the relevance of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention’s risks and benefits.

The issues presented here represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has unique methodological aspects.

1. Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to help ensure adequate numbers of patients are enrolled to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias)
- Co-interventions or provision of care apart from the intervention under evaluation (confounding)
- Differential assessment of outcome (detection bias)
- Occurrence and reporting of patients who do not complete the study (attrition bias)

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study's selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess the evidence.

2. Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens, and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease, and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing, and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage decisions for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation), and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations because one of the goals of our determination process is to assess health outcomes. We are interested in the results of changed patient management not just altered management. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

3. Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Improved health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. For most determinations, CMS evaluates whether reported benefits translate into improved health outcomes. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

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[1] A humanitarian use device (HUD) is a device "intended to benefit patients in the treatment and diagnosis of diseases or conditions that affect fewer than 4,000 individuals in the United States" (Federal Food, Drug and Cosmetic Act) per year. When considering HUDs for an HDE, which authorizes marketing of an HUD, the FDA requires the device to meet the safety but not effectiveness requirement. Additionally, no comparable device can be available to treat or diagnose the disease or condition other than another HDE approved HUD or a device being studied under an FDA approved Investigational Device Exemption (IDE).

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